

Highly diastereoselective additions of methoxyallene and acetylenes to chiral α -keto amides†

So Won Youn, Yong Hae Kim,* Jeong-Wook Hwang and Youngkyu Do*

Center for Molecular Design & Synthesis, School of Molecular Science, Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejeon, 305-701, Korea. E-mail: kimyh@mail.kaist.ac.kr

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α -Keto amides bearing (S)-indoline chiral auxiliaries reacted with lithiated methoxyallene or lithium acetylides to produce the corresponding dihydrofuranones **7** through formation of the tertiary α -hydroxy allenes, or tertiary α -hydroxy acetylenes, respectively, at -78°C with high diastereoselectivities (up to $>99\%$ de).

A number of diastereoselective nucleophilic additions of organometallic reagents to α -keto amides¹ bearing appropriate chiral auxiliaries have been reported as useful methods for the synthesis of optically active tertiary α -hydroxy acid derivatives, which are valuable for the asymmetric syntheses of medicinal agents and natural products.² Creating a tertiary alcohol center in which the stereochemistry can be controlled by a defined chiral environment in the addition of organometallic reagents to ketones still represents a significant challenge.³

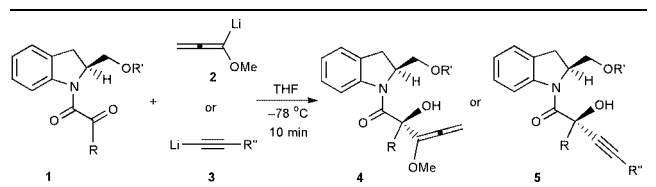
Lithiated methoxyallene^{4–6} is a promising nucleophile because the products produced by its addition to carbonyl compounds^{7–8} can be converted into a variety of interesting compounds such as enones⁹ or dihydrofuran derivatives.¹⁰ In particular chiral propargylic alcohols¹¹ are useful intermediates in the synthesis of natural products.^{2,12} Although a number of stereoselective additions of acetylides to aldehydes^{11a–c} have been reported, asymmetric addition of acetylides to ketones to produce chiral tertiary alcohols is little known.^{11d,e} A highly enantioselective addition of cyclopropylacetylide to aryltrifluoromethyl ketone as a special substrate has been reported as the first example.^{11d,e} However, a general method to prepare chiral tertiary α -hydroxy acetylenes has not yet been reported.

Recently, we reported that chiral α -keto amides derived from (S)-indoline-2-carboxylic acid resulted in high stereoselectivity in stereocontrolled additions of organometallics^{1b} and allylation.^{1c} On the supposition that these chiral α -keto amides might be good chiral auxiliaries, we examined the diastereoselective additions of lithiated methoxyallene **2** and lithium acetylides **3** to various chiral α -keto amides **1**.

The lithiated methoxyallene **2** was generated by treatment of methoxyallene (2.5 eq.) with *n*-BuLi (2.0 eq.) in THF at -78°C for 30 min.^{7b} Lithium acetylide **3** was prepared by addition of *n*-BuLi (1.5 eq.) to a solution of acetylene (1.7 eq.) in THF at 0°C , followed by cooling to -78°C after 30 min.^{11a} Lithiated methoxyallene or lithium acetylide was reacted with α -keto amides at -78°C in THF. Since the allene adducts **4** are generally labile^{7b,c} so giving low yields (Table 1), the crude product **4** was reacted to obtain **6** without purification. Two equivalents of **2** were added to **1** at -78°C in THF. The reaction mixture was stirred for 10 min at -78°C and then quenched with distilled water. Extraction with CH_2Cl_2 , drying over MgSO_4 , and concentration gave crude product **4**, which was treated with a solution of *t*-BuOK (0.5 eq.) in DMSO at 50°C . The reaction mixture was stirred for 1 h and then quenched with H_2O . Extraction with Et_2O , drying over MgSO_4 , and concentra-

tion gave the crude residue, which was purified by column chromatography on SiO_2 to give dihydrofuran derivatives **6** which were treated with 5% HCl and extracted with diethyl ether and EtOAc at pH 11. The combined organic layers were dried over MgSO_4 and concentrated to give dihydrofuranones **7**. The results obtained are summarized in Table 2.

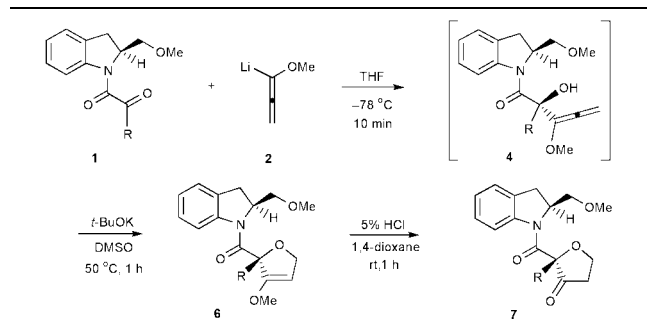
Table 1 Diastereoselective additions of lithiated methoxyallene **2** and lithium acetylides **3** to chiral α -keto amides **1**



Run	Substrate	R	R'	R''	Product	Yield (%) ^a	dr ^b
1	1a	Me	Me	—	4a	42	99:1
2	1b	Et	Me	—	4b	54	94:6
3	1c	<i>n</i> -Hex	Me	—	4c	45	98:2
4	1d	Ph	Me	—	4d	56	96:4
5	1e	Me	SiMe ₂ Bu- <i>t</i>	—	4e	32	80:20
6	1f	Ph	SiMe ₂ Bu- <i>t</i>	—	4f	33	83:17
7	1a	Me	Me	Ph	5a	71	98:2
8	1b	Et	Me	Ph	5b	91	94:6
9	1d	Ph	Me	Ph	5c	53	95:5
10	1e	Me	SiMe ₂ Bu- <i>t</i>	Ph	5d	62	99:1
11	1a	Me	Me	CH ₂ OMe	5e	72	99:1
12	1a	Me	Me	<i>n</i> -Bu	5f	88	99:1
13	1a	Me	Me	SiMe ₃	5g ^c	66	$>99:1$

^a Isolated yields. ^b Determined by HPLC (Daicel chiral OD column). ^c R'' = H:SiMe₃ was removed.

Table 2 Transformation of crude products **4** to dihydrofuran derivatives **6** and 3(2*H*)-dihydrofuranones **7**



Run	R	6		7	
		Yield (%) ^{a,b}	dr ^c	Yield (%) ^a	dr ^c
1	Me (1a)	33 (6a)	$>99:1$	80 (7a)	$>99:1$
2	Et (1b)	41 (6b)	$>99:1$	76 (7b)	$>99:1$
3	<i>n</i> -Hex (1c)	35 (6c)	$>99:1$	75 (7c)	$>99:1$
4	Ph (1d)	44 (6d)	$>99:1$	78 (7d)	$>99:1$

^a Isolated yields. ^b Overall yields from **1**. ^c Determined by ¹H NMR.

† Electronic supplementary information (ESI) available: synthesis and spectroscopic data for **4b**, **5g**, **6b** and **7b**. See <http://www.rsc.org/suppdata/cc/b1/b100355k/>

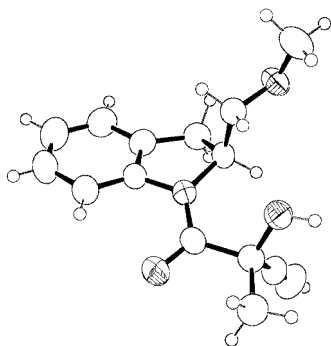
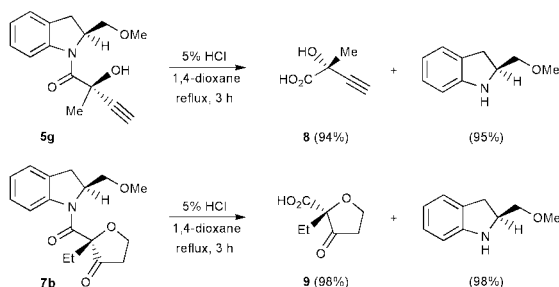


Fig. 1 X-Ray structure of **5g**.

The purified products **4**, **5** and **6** were identified by ^1H , ^{13}C NMR, $^{7b-d}$ IR and MS. The ratios of diastereomers were determined by HPLC using a chiral OD column. The absolute configuration of **5g** was determined by comparison of the specific rotation of **8** ($[\alpha]_{\text{D}}^{25} -40.2^\circ$, $c = 1.7$, acetone) with the literature value¹³ ($[\alpha]_{\text{D}}^{24} -41.0^\circ$, $c = 10$, acetone) and its structure determined by X-ray analysis (Fig. 1).¹⁴ The ratios of diastereomers were unaltered during the process. Compound **8** has been found in plant growth regulators^{2e} and highly enantiomeric excess synthesis of **8** has not been reported previously.

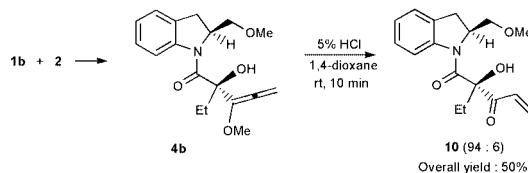
Enol ethers of 2,5-dihydrofuran derivatives **6** were readily hydrolyzed by HCl solution ($\text{H}_2\text{O}:\text{1,4-dioxane} = 10:1$) to provide the corresponding 3(2*H*)-dihydrofuranones **7** in good yields (75–80%), which are interesting intermediates as analogues of muscarone.^{15b} Their structural element appears in other biologically active compounds¹⁵ and their transformation to certain deoxy sugar derivatives can be performed. The indoline α -keto amides have a great advantage in terms of cleavage of the amide bond to give chiral products and recover the indoline chiral auxiliary.^{1b,c,16} The cleavage of the amide bond of indoline amides is much easier than that of alkyl amides such as proline amides. For instance, the chiral products **5g** or **7b** were readily hydrolyzed with 5% HCl in 1,4-dioxane under reflux for 3 h to give the corresponding 2-hydroxy-2-methylbut-3-ynoic acid **8** or 2-ethyl-3(2*H*)-dihydrofuranone-2-carboxylic acid **9** in 94–98% yields, respectively, as shown in Scheme 1. The chiral auxiliary was recovered in 95–98% yield without loss of optical purity. Earlier work^{11d,e} on asymmetric addition of acetylide to a ketone (not a chiral auxiliary) gave one chiral tertiary alcohol from a specific ketone leading to one compound. Our method, however, provides a general methodology to produce chiral tertiary α -hydroxy carboxylic acid acetylenes.



Scheme 1

Conversion of the hydroxyalkylated allenes into the α,β -unsaturated ketones under acidic conditions is also a useful reaction.⁹ It is noteworthy that treatment of **4b** with 5% HCl provided enone **10** within 10 min at 25°C as shown in Scheme 2. The ratio of diastereomers was also unaltered during hydrolysis. The enone moiety may be an interesting precursor for Michael-type additions or cycloadditions.¹⁷

In summary, it has been demonstrated that the reaction of α -keto amides derived from (*S*)-indoline-2-carboxylic acid with lithiated methoxyallene or lithium acetylide can provide useful



Scheme 2

intermediates, chiral tertiary α -hydroxy acid derivatives with high diastereoselectivities.

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